Regorafenib (Stivarga)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Regorafenib received FDA-approval for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with a fluoropyrimidine agent, oxaliplatin, irinotecan, anti-VEGF therapy and, if KRAS wild type, an anti-EGFR agent. Most recently, the FDA granted the indication of the treatment of patients with locally advanced, unresectable or metastatic Gastrointestinal Stromal Tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib maleate.

Efficacy in mCRC:

- In a phase 3 trial, study participants had adenocarcinoma of the colon or rectum and had progression and/or intolerance of multiple therapies; the mean age of this group was 61 years. Males made up 60% of the population, 80% were Caucasian and all had an ECOG PS of 0 or 1.
- The median OS rates were 6.4 vs. 5 months, respectively, comparing regorafenib vs. placebo arms; HR 0.77; 95% CI 0.64-0.94; p=0.0052. A greater OS effect was noted on those with colon (HR 0.70; 95% CI 0.56-0.89) vs. rectal disease (HR 0.95; 95% CI 0.62-1.43).
- The median PFS rates were 1.9 vs. 1.7 months (HR 0.49; 95% CI 0.42-0.58; p< 0.0001)
- ORR was not significantly different between the groups; no one achieved a CR. A total of 6 patients had a partial response (5 regorafenib vs. 1 placebo) giving ORR of 1.0 vs. 0.4% respectively (p=0.19).
- The mean duration of treatment in the regorafenib vs. placebo arms was 12 vs. 8 weeks. Those assigned regorafenib received 79% of their planned doses, while placebo-treated patients received 90% of their planned doses.
- Health-related Quality of Life (HRQOL) was considered a tertiary endpoint. The results indicate the deterioration in QOL was similar in both regorafenib and placebo arms. The assessment of health utility indicated that no clinically meaningful difference between the start to end of treatment existed in either group.

Efficacy in GIST

- Efficacy in GIST was evaluated in a phase 3 trial that included adult patients with metastatic or unresectable GIST who had received prior therapy with imatinib and sunitinib. This population had an ECOG PS of 0 or 1; median age was 60 years; 64% male; 68% Caucasian and 25% Asian.
- The median PFS rates were 4.8 vs. 0.9 months, respectively, in the regorafenib vs. placebo arms; HR 0.27; 95% CI 0.19-0.39; p<0.0001. After progression, 85% of patients in the placebo arm crossed over to regorafenib. The median PFS for those crossover

patients was ~ 5 months. There was no difference in OS: 22 vs. 26 events; HR 0.77; 95% CI 0.42-1.41; p=0.199.

- All subgroups showed benefit from regorafenib, except for the subset of patients with imatinib duration < 6 months.
- The ORR in regorafenib vs. placebo arms was 4.5 vs. 1.5%; no complete responses were noted. Stable disease was noted in 71 vs. 33% of patients in the regorafenib vs. placebo arms. DCR was 53 vs. 9%; these results suggest that regorafenib has a disease-stabilizing effect.

Safety in mCRC

- Treatment-related adverse events (all grades) were reported in 93 vs. 61% of regorafenib vs. placebo-treated patients. Adverse events led to dose-modification in 67 vs. 23% in the regorafenib vs. placebo arms, respectively. The most common adverse events reported in the regorafenib arm were fatigue (47% all; 9% grade 3), hand-foot syndrome reaction (47% all; 17% grade 3), diarrhea (34% all; 7% grade 3), hypertension (28% all; 7% grade 3) and rash (26% all; 6% grade 3), while fatigue and anorexia were most common among those receiving placebo.
- Serious (grade 3) adverse events were more common in the regorafenib arm with 51 vs. 12% experiencing grade 3 toxicity. Grade 4 toxicity was slightly higher with regorafenib at 3% vs. 2% of those receiving placebo. Treatment-related deaths were reported in 2% of regorafenib vs. 1% of placebo-treated patients. Causes of death due to regorafenib included pneumonia, GI bleed, GI obstruction, pulmonary hemorrhage, seizure and sudden death.

Safety in GIST

- Dose-modifications due to treatment-related Adverse Events (AEs) occurred in 72 vs. 26% of regorafenib vs. placebo-treated patients, respectively. Drug-related AEs (any grade) occurred in 98 vs. 69% of regorafenib vs. placebo-treated patients, yet discontinuation of therapy due to drug-related AEs were only reported in 6 vs. 8% of those with GIST.
- The most common AE of any grade reported in the GRID trial was Hand-Foot Syndrome Reaction (HFSR), which occurred in 56 vs. 14% of regorafenib vs. placebo patients. Severe AEs (grade 3-5) were reported in more regorafenib-treated patients: 61 vs. 14%. These events included hypertension (23%), HFSR (20%) and diarrhea (5%).
- Drug-related deaths occurred similarly in both groups: 2 vs. 2%. Causes of death related to regorafenib included cardiac arrest and hepatic failure. Fatigue was the cause of death in the placebo group.

Determination of Clinical Benefit

Table 1. Determination of Clinical Benefit in mCRC

Outcome in clinically significant area: mCRC	mCRC: Median OS 6.4 vs. 5 months mCRC: Median PFS 1.9 vs. 1.7 months
Effect Size	HR 0.77; 95% CI 0.64-0.94; p=0.0052 for OS HR 0.49; 95% CI 0.42-0.58; p<0.0001 for PFS
Potential Harms	Grade 3-4 toxicity includes asthenia/fatigue (15 vs. 9%); HFSR/PPE (17 vs. 0%); Diarrhea (8 vs. 2%); HTN (8 vs. <1%); Rash (6 vs. <1%)
Net Clinical Benefit	Minimal (modest benefit; high toxicity)

Table 2. Determination of Clinical Benefit in GIST

Outcome in clinically significant area: GIST	GIST: Median PFS 4.8 vs. 0.9 months 85% crossed over to Regorafenib arm; The median PFS for those crossover patients was ~ 5 months. No difference in OS: 22 vs. 26 events
Effect Size	HR 0.27; 95% CI 0.19-0.39; p<0.0001 for PFS HR 0.77; 95% CI 0.42-1.41; p=0.199 for OS
Potential Harms	Grade 3-4 toxicity includes HFSR (20 vs. 0%); HTN (23 vs. 3%), Diarrhea (5 vs. 3%)
Net Clinical Benefit	Minimal (modest benefit; high toxicity)

Introduction[3, 5, 6, 7]

It is estimated that approximately 143,000 new cases of colon and rectal cancer would be diagnosed in the U.S. in 2012 and result in 52,000 deaths. As the population ages, more cases are diagnosed. The lifespan of the patient with colorectal cancer has increased from the earlier days when only 5-fluorouracil was the leading therapeutic option. Overall survival rates, reported from phase 3 trials, have been extended from 12 months to 24 months. This increase in survival has been attributed to the activity of new agents in CRC.

Gastrointestinal Stromal Tumor (GIST) is the most common sarcomas from the GI tract. The annual incidence of GIST in the United States is at least 4000 to 6000 new cases. GISTs occur predominantly in middle-aged and older individuals. It is rare in those under the age of 40. An analysis of SEER registry data reports the mean age at diagnosis was 63 years. Disease found in its early stages is surgically resectable. It has been estimated that greater than 40% will recur and metastasize. Median disease-specific survival of patients with metastatic GIST (N = 94) is estimated to be 19 months. Approximately 85% of GIST is due to mutations in the proto-oncogene KIT and 8% due to mutations in platelet-derived growth factor receptor α (PDGFRA). For these reasons, targeted tyrosine kinase inhibitors have an established role in the treatment of GIST.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating regorafenib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,4]

- Regorafenib is structurally related to sorafenib. It differs by the additional fluorine atom located in the central phenyl ring.
- *In vitro* assays show that regorafenib is a more potent inhibitor of VEGFR-2, PDGFR-β, FGFR-1 and c-kit than sorafenib.
- Regorafenib also inhibits TIE-2, therefore is thought to have broader antiangiogenic properties.

Pharmacokinetics

Absorption: In a population of patients with advanced solid tumors, a dose of regorafenib 160mg was given. The geometric mean peak plasma level (Cmax) of 2.5 µg/ml and the geometric mean area under the plasma concentration vs. time curve (AUC) of 70.4 µg*h/ml was reached at a median of 4 hours. At steady state, the AUC increases less than dose proportionally at doses greater than 60 mg with a Cmax value of 3.9 µg/ml and AUC value of 58.3 µg/ml with the coefficient of variation between 35-44%.

When comparing tablets to an oral solution, the mean relative bioavailability is 69-83%.

A food-effect study was conducted to evaluate the impact of food on regorafenib kinetic parameters. In 24 healthy male participants, a single 160 mg dose was given in a fasted, high-fat and low-fat state.

When comparing the high-fat meal to the fasted state:
The high-fat meal increased the mean AUC of regorafenib by 48%.
Metabolites, M-2 and M-5, had reduced mean AUC values by 20 and 51%.

When comparing the low-fat meal to the fasted state:
A low-fat meal increased the mean AUC of regorafenib by 36%.
Metabolites, M-2 and M-5, had increased mean AUC values by 40 and 23%.
Regorafenib was administered with a low-fat meal in the phase 3 study.

Distribution: Regorafenib is distributed via enterohepatic circulation and is highly protein bound (99.5%).

Metabolism: Regorafenib is metabolized by CYP3A4 and UGT1A9, with the primary metabolites being M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl). These metabolites have similar *in vitro* activity, steady-state concentrations and are also highly protein bound.

Elimination: The geometric mean elimination half-lives for regorafenib and metabolites (M-2, M-5) following a single 160 mg dose are as follows: 28 (14-58) hours; 25 (14-32) hours; 51 (32-70) hours, respectively.

Roughly 71% of an oral 120mg radiolabeled dose of regorafenib was excreted in feces (47% parent; 24% metabolites) and 19% excreted in urine (17% as glucuronides) within 12 days after administration.

FDA Approved Indication(s)

Regorafenib is FDA-approved for the treatment of patients with metastatic colorectal cancer (mCRC) who have progressed after receiving fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, as well as anti-VEGF therapy and anti-EGFR therapy (if KRAS wild-type).

At the end of August 2012, the FDA granted priority review to the New Drug Application (NDA) that was filed for regorafenib to treat metastatic and/or resectable GIST that has progressed despite treatment with two kinase inhibitors. This priority review was based upon results from the GRID study[3].

In February, 2013 the FDA approved regorafenib for the treatment of patients with locally advanced, unresectable or metastatic GIST who have been previously treated with imatinib mesylate and sunitinib malate.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Clinical trials listed on www.clinicaltrials.gov are studying the effects of regorafenib in combination with the FOLFIRI (fluorouracil, leucovorin, irinotecan) regimen as second-line treatment of mCRC, in combination with the FOLFOX6 (fluorouracil, leucovorin, oxaliplatin) regimen as first-line treatment of mCRC, treatment of hepatocellular carcinoma after sorafenib failure and as a therapeutic option in renal cell carcinoma.

Current VA National Formulary Alternatives

mCRC: Best Supportive Care
GIST: Best Supportive Care

Dosage and Administration in mCRC and GIST

Regorafenib is an oral formulation. The recommended dose is 160 mg (4 x 40 mg tablets) daily for 21 days of each 28-day cycle. Treatment is to be continued until disease progression or unacceptable toxicity.

Regorafenib is packaged in 3 bottles, each containing 28 tablets for a total of 84 tablets per package. Each bottle provides a 7-day supply of 160 mg regorafenib daily. An entire package would provide one cycle (21 days). Due to the concern for moisture affecting the pharmacokinetic profile of regorafenib, drug should be stored in the original bottle with the provided desiccant and discarded 28 days after opening.

The dose should be taken at the same time each day.
Swallow the tablets whole with a low-fat breakfast (contains < 30% fat).
Missed doses should not be made up with the next day's dose (do not take two doses in one day).

Dose modifications
Interrupt regorafenib dosing for the following:

- Grade 2 Hand-Foot Skin Reaction (HFSR)/Palmar-Plantar Erythrodysesthesia (PPE) that is recurrent or does not improve within 7 days despite a dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR
- Symptomatic Grade 2 hypertension
- Any Grade 3 or 4 adverse reaction

Reduce regorafenib dose to 120 mg for the following:

- First occurrence of Grade 2 HFSR of any duration
- After recovery of any Grade 3 or 4 adverse reaction
- For Grade 3 AST/ALT elevation; resume only if potential benefit outweighs the risk of hepatotoxicity

Reduce regorafenib dose to 80 mg for the following:

- Re-occurrence of Grade 2 HFSR at the 120 mg dose
- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity)

Discontinue regorafenib permanently for the following:

- Failure to tolerate the 80 mg dose
- Any occurrence of AST or ALT more than 20 times the upper limit of normal (ULN)
- Any occurrence of AST or ALT more than 3 times the ULN with concurrent bilirubin more than 2 times ULN
- Any re-occurrence of AST or ALT more than 5 times ULN despite dose reduction to 120 mg
- Any Grade 4 adverse reaction; resume only if potential benefit outweighs the risk

Efficacy

Efficacy Measures in mCRC (see Appendix 1: Approval Endpoints)

The endpoints evaluated to determine the efficacy of regorafenib in the treatment of metastatic colorectal cancer include the following:

Primary endpoint:	Overall Survival (OS)
Secondary endpoints:	Progression-Free Survival (PFS)
	Objective Response Rate (ORR)
	Disease Control Rate (DCR) defined as the proportion of patients with a best response of complete or partial response or stable disease; assessment of stable disease made at least 6 weeks after randomization.
Tertiary endpoints:	Duration of Response (DOR)
	Stable Disease (SD)
	Health-Related Quality of Life (HRQOL)
	EuroQol five dimension (EQ-5D) assessed health utility values

Efficacy Measures in GIST (see Appendix 1: Approval Endpoints)

Primary endpoint:	Progression-Free Survival (PFS)
Secondary endpoints:	Overall Survival (OS)
	Time to Progression (TTP)
	Objective Response Rate (ORR)

	Disease Control Rate (DCR) defined as the proportion of patients with a best response of complete or partial response or stable disease; assessment of stable disease made at least 12 weeks after randomization.
Tertiary endpoints:	Health-Related Quality of Life (HRQOL) Pharmacokinetics Secondary PFS Biomarker assessment

Summary of efficacy findings in mCRC

- Efficacy of regorafenib in the treatment of mCRC was evaluated in a randomized, placebo-controlled, multicenter, international phase 3 trial that involved 114 centers within 16 countries.
- Study participants included adult patients with a diagnosis of adenocarcinoma of the colon or rectum who had received standard therapies that included the following drugs: a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab if KRAS-WT tumors. In addition, these patients had ECOG PS of 0 or 1.
- A total of 760 patients were randomized 2:1 to regorafenib (500) or placebo (253); all patients received best supportive care; regorafenib was started at 160mg orally daily for 21 days, and repeated every 28 days until disease progression or intolerable toxicity.
- Demographically, this population had a median age of 61 years; 60% male; 80% Caucasian. The majority were KRAS mutated and BRAF wild type. Roughly 50% had received at least 4 prior therapies for metastatic disease with a median time from diagnosis of 30 months.
- The median OS rates were 6.4 vs. 5 months, respectively, comparing regorafenib vs. placebo arms; HR 0.77; 95% CI 0.64-0.94; p=0.0052. A greater OS effect was noted on those with colon (HR 0.70; 95% CI 0.56-0.89) vs. rectal disease (HR 0.95; 95% CI 0.62-1.43).
- The median PFS rates were 1.9 vs. 1.7 months (HR 0.49; 95% CI 0.42-0.58; p< 0.0001)
- ORR was not significantly different between the groups; no one achieved a CR, but disease stability was noted with a DCR of 41 vs. 15%, respectively, in the regorafenib vs. placebo arms (p<0.001).
- The mean duration of treatment in the regorafenib vs. placebo arms was 12 vs. 8 weeks. Those assigned regorafenib received 79% of their planned doses, while placebo-treated patients received 90% of their planned doses.
- Treatment-related adverse events were reported in 93 vs. 61% of regorafenib vs. placebo-treated patients. Adverse events led to dose-modification in 67 vs. 23% in the regorafenib vs. placebo arms, respectively. The most common adverse events reported in the regorafenib arm were fatigue and hand-foot syndrome reaction (HFSR), while fatigue and anorexia were most common among those receiving placebo.
- Serious (grade 3) adverse events were more common in the regorafenib arm with 51 vs. 12% experiencing grade 3 toxicity. Grade 4 toxicity was slightly higher with regorafenib at 3% vs. 2% of those receiving placebo. Treatment-related deaths were reported in 2% of regorafenib vs. 1% of placebo-treated patients. Causes of death due to regorafenib included pneumonia, GI bleed, GI obstruction, pulmonary hemorrhage, seizure and sudden death.
- Health-related Quality of Life (HRQOL) was considered a tertiary endpoint. The results indicate the deterioration in QOL was similar in both regorafenib and placebo arms. The assessment of health utility indicated that no clinically meaningful difference between the start to end of treatment existed in either group.

Summary of efficacy findings in GIST

- The efficacy of regorafenib in the treatment of GIST was evaluated in a randomized, placebo-controlled, multicenter, phase 3, international trial that included 57 centers in 17 countries.
- Study participants included adult patients with metastatic and/or unresectable GIST who had received prior therapy with imatinib and sunitinib and an ECOG performance status of 0 or 1.
- A total of 199 patients were randomized 2:1 to regorafenib 160 mg or placebo orally daily for 3 weeks, followed by one week off. A complete cycle was 4 weeks. Treatment continued until progressive disease or unacceptable toxicity. At PD, the placebo group was permitted to crossover to the regorafenib arm.
- Demographically, this population had a median age of 60 years (range, 48-67); 64% male; 68% Caucasian; 25% Asian; ~ 42% received more than 2 lines of prior systemic anticancer therapy; the placebo arm had a 83% of their patients receive imatinib for greater than 18 months, while the regorafenib arm only had 67% receive imatinib for that period of time.
- The median PFS rates were 4.8 vs. 0.9 months, respectively, in the regorafenib vs. placebo arms; HR 0.27; 95% CI 0.19-0.39; $p<0.0001$. After progression, 85% of patients in the placebo arm crossed over to regorafenib. The median PFS for those crossover patients was ~ 5 months. There was no difference in OS: 22 vs. 26 events; HR 0.77; 95% CI 0.42-1.41; $p=0.199$.
- All subgroups showed benefit from regorafenib, except for the subset of patients with imatinib duration < 6 months.
- The ORR in regorafenib vs. placebo arms was 4.5 vs. 1.5%; no complete responses were noted. Stable disease was noted in 71 vs. 33% of patients in the regorafenib vs. placebo arms. DCR was 53 vs. 9%; these results suggest that regorafenib has a disease-stabilizing effect.
- Drug-related Adverse Events (AEs) were reported in 98 vs. 69% of regorafenib vs. placebo-treated patients. The most common AE (any grade) was Hand-Foot Syndrome Reaction (HFSR): 56 vs. 14%, respectively.
- Grade 3-5 AEs were greater in regorafenib-treated patients: 61 vs. 14% and included HTN (23%), HFSR (20%), diarrhea (5%). Serious AE included abdominal pain, fever and dehydration.
- Dose-modification due to AEs occurred in 72 vs. 26% of regorafenib vs. placebo-treated patients. Drug discontinuation due to AEs occurred in 6 vs. 8%.

For further details on the efficacy results of the clinical trials, refer to *Appendix 1: Approval Endpoints*

Table 3. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.

For further details on the efficacy results of the clinical trials, refer to *Appendix 2: Clinical Trials*.

Adverse Events (Safety Data) in mCRC

The safety of regorafenib was evaluated in the phase 3 trials where 500 patients received regorafenib and 253 received placebo. Adverse events led to dose-modification in 67% of regorafenib-treated patients. Drug-related events led to discontinuation of regorafenib therapy in 8.2% of treated patients, compared to 1.2% of those receiving placebo. Dermatologic toxicity was the most common reason for drug discontinuation.

Adverse reactions noted in ≥ 10% of patients receiving regorafenib are listed in Table 4 below.

Table #4 Adverse Drug Reactions (ADRs) reported in patients receiving regorafenib and reported more commonly than patients receiving placebo

ADR	Regorafenib All grade (%)	Regorafenib Grades 3-5 (%)	Placebo All grade (%)	Placebo Grades 3-5 (%)
Asthenia/fatigue	64	15	46	9
Pain	29	3	21	2
Fever	28	2	15	0
↓ appetite/food intake	47	5	28	4
HFSR/PPE	45	17	7	0
Rash	26	6	4	< 1
Diarrhea	43	8	17	2
Mucositis	33	4	5	0
Weight loss	32	< 1	10	0
Infection	31	9	17	6
HTN	30	8	8	<1
Hemorrhage	21	2	8	<1
Dysphonia	30	0	6	0
Headache	10	<1	7	0

Laboratory abnormalities observed in the phase 3 trial are included in Table 2 below.

Table #5: Laboratory abnormalities reported by Grothey et al.

Parameter	Regorafenib plus BSC			Placebo plus BSC		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Anemia	79	5	1	66	3	0
Thrombocytopenia	41	2	<1	17	<1	0
Neutropenia	3	1	0	0	0	0
Lymphopenia	54	9	0	34	3	0
Hypocalcemia	59	1	<1	18	1	0
Hypokalemia	26	4	0	8	<1	0
Hyponatremia	30	7	1	22	4	0
Hypophosphatemia	57	31	1	11	4	0
Hyperbilirubinemia	45	10	3	17	5	3
Increased AST	65	5	1	46	4	1
Increased ALT	45	5	1	30	3	<1
Proteinuria	60	<1	0	34	<1	0
Increased INR	24	4	n/a	17	2	n/a
Increased lipase	46	9	2	19	3	2
Increased amylase	26	2	<1	17	2	<1

Deaths and Other Serious Adverse Events

Serious adverse events occurring in clinical trial participants who have received regorafenib include hepatotoxicity, hemorrhage and gastrointestinal perforation.

Common Adverse Events

The most common adverse drug events (≥ 30%) occurring in those receiving regorafenib are: asthenia/fatigue, decreased appetite, HRSR/PPE, diarrhea, mucositis, weight loss, infection, hypertension and dysphonia.

Other Adverse Events
Refer to Table 4.

Tolerability
Patients who received regorafenib in the mCRC clinical trial setting had a higher rate of drug discontinuation due to adverse events. Grothey et al. report that regorafenib-treated patients received 79% of their planned doses as compared to the placebo-treated patients, who received 90% of their doses.[2] Dose-modifications in the regorafenib vs. placebo arms were made in 76 vs. 38%, respectively.

Adverse Events (Safety Data) in GIST

The safety of regorafenib was evaluated in the phase 3 trial where 132 patients received regorafenib and 66 received placebo. Adverse events led to dose-interruptions in 58% of regorafenib-treated patients and dose-reductions in 50%. Drug-related events led to discontinuation of regorafenib therapy in 2.3% of treated patients, compared to 1.5% of those receiving placebo. The median duration of therapy was 22.9 weeks (range, 0.1-50.9) in patients receiving regorafenib.

Adverse reactions noted in ≥ 10% of patients receiving regorafenib are listed in Table 6 below.

Table #6 Adverse Drug Reactions (ADRs) reported in patients receiving regorafenib and reported more commonly than patients receiving placebo

ADR	Regorafenib All grade (%)	Regorafenib Grades 3-5 (%)	Placebo All grade (%)	Placebo Grades 3-5 (%)
HRSR/PPE	67	22	15	2
Rash	30	7	3	0
Alopecia	24	2	2	0
Asthenia/Fatigue	52	4	39	2
Fever	21	0	11	2
Hypertension	59	28	27	5
Hemorrhage	11	4	3	0
Diarrhea	47	8	9	0
Mucositis	40	2	8	2
Nausea	20	2	12	2
Vomiting	17	<1	8	0
Dysphonia	39	0	9	0
Infection	32	5	5	0
↓ appetite/food intake	31	<1	21	3
Hypothyroidism	18	0	6	0
Headache	16	0	9	0
Weight loss	14	0	8	0
Musculoskeletal stiffness	14	0	3	0

Laboratory abnormalities observed in the phase 3 trial are included in Table 7 below.

Table #7: Laboratory abnormalities reported by Demetri et al.

Parameter	Regorafenib plus BSC (n=132)			Placebo plus BSC (n=66)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Thrombocytopenia	13	1	0	2	0	2
Neutropenia	16	2	0	12	3	0
Lymphopenia	30	8	0	24	3	0
Hypocalcemia	17	2	0	5	0	0

Hypokalemia	21	3	0	3	0	0
Hypophosphatemia	55	20	2	3	2	0
Hyperbilirubinemia	33	3	1	12	2	0
Increased AST	58	3	1	47	3	0
Increased ALT	39	4	1	39	2	0
Proteinuria	33	3	-[a]	30	3	-[a]
Increased lipase	14	0	1	5	0	0

[a] No Grade 4 denoted in CTCAE, v4.0

For further details on the safety results of the clinical trials, refer to *Appendix 2: Clinical* Trials.

Contraindications

None.

Warnings and Precautions

Regorafenib contains a boxed warning regarding the risk of hepatotoxicity, as severe and sometimes fatal hepatotoxicity was observed in the clinical trials. Hepatic function (AST, ALT, bilirubin) should be monitored prior to and during treatment with regorafenib. Dosing should be interrupted and then reduced or discontinued for elevated liver function tests or hepatocellular necrosis, depending on severity and persistence.

Hepatotoxicity

Across all clinical trials, liver injury with fatal outcome due to regorafenib therapy was reported in 0.3% of 1200 patients. Review of liver biopsy results indicate that hepatocyte necrosis with lymphocyte infiltration was apparent. Grothey et al. report that hepatic failure was fatal in 1.6% vs. 0.4% of patients in the regorafenib vs. placebo arm, respectively. Demetri et al, reported fatal hepatic failure in 0.8% of patients in the regorafenib arm.

Liver function tests, including AST, ALT and bilirubin, should be evaluated prior to starting regorafenib therapy and monitored at least every 2 weeks during the first 2 months of treatment. Monitoring can then continue on a monthly or more frequent basis, if needed. Patients with elevated LFT's should be monitored weekly until lab parameters have improved to less than 3 times the ULN or baseline level.

Refer to **Dosing and Administration** for specific guidance on when to hold regorafenib and how to resume therapy.

Hemorrhage

Patients receiving regorafenib in the clinical trial setting experienced an increased incidence of hemorrhage. Grothey et al. report 21 vs. 8% of patients receiving regorafenib vs. placebo, respectively, experienced grades 1-5 bleeding. The data by Demetri et al. note the incidence of grades 1-5 hemorrhage in GIST patients was 11 vs. 3% in regorafenib vs. placebo arms. Fatal bleeding events occurred in 0.6% (4/632) of regorafenib-treated patients. These events involved the respiratory, gastrointestinal or genitourinary tracts.

Regorafenib should be permanently discontinued in patients with severe or life-threatening bleed. Monitor INR values more frequently in those receiving warfarin.

Dermatologic Toxicity

Patients taking regorafenib experienced an increased incidence of dermatologic conditions, specifically hand-foot skin reaction (HFSR) which is also known as palmar-plantar erythrodysesthesia (PPE), and rash. The onset of dermatologic toxicity was noted in the first cycle of treatment.

Table#8. Comparison of Dermatologic Toxicity

	Regorafenib In mCRC	Regorafenib in GIST	Placebo In mCRC	Placebo In GIST
Overall HFSR (%)	45	67	7	12
Grade 3 HRSR (%)	17	22	0	0
Overall rash (%)	26	30	4	3
Grade 3 rash (%)	6	7	<1	0

Depending on the severity of the effect, regorafenib therapy may be held, dose-reduced or permanently discontinued. Manage dermatologic symptoms with supportive measures.

Hypertension

Regorafenib-treated patients experienced an increased incidence of hypertension within the clinical trials. The onset of hypertension occurred during the first cycle of treatment in most patients.

Table#9. Comparison of Hypertension Incidence

	Regorafenib in mCRC	Regorafenib in GIST	Placebo in mCRC	Placebo in GIST
Overall hypertension	28	59	6	27
Grades 3, 4	7	24	1	3

Do not initiate regorafenib until the blood pressure is adequately controlled. Blood pressure should be monitored weekly for the first 6 weeks of treatment, then with every cycle, unless needed more frequently. Patients with severe or uncontrolled hypertension should have regorafenib temporarily or permanently withheld. See Dosing and Administration for guidance on holding therapy for hypertension.

Cardiac Ischemia and Infarction

Patients treated with regorafenib experienced an increased incidence of myocardial ischemia and infarction (1.2 vs. 0.4%, regorafenib vs. placebo-treated patients, respectively).

Hold regorafenib therapy in those who develop new or acute onset cardiac ischemia or infarction. Reinstituting regorafenib therapy after resolution of acute cardiac ischemic events should occur only if the potential benefits of therapy outweigh the risks of further cardiac damage.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS was reported in one of 1100 patients treated with regorafenib across all clinical trials. If RPLS is suspected, confirm the diagnosis via MRI and discontinue regorafenib therapy in those who develop the Syndrome.

Gastrointestinal Perforation or Fistula

Gastrointestinal perforation or fistula was reported in 0.6% of 1100 patients treated with regorafenib across all clinical trials. Regorafenib should be permanently discontinued in anyone who develops gastrointestinal perforation or fistula.

Wound Healing Complications

There have been no formal studies on the effects of regorafenib on wound healing. Since VEGF inhibitors are known to impair wound healing, treatment with regorafenib should be stopped at least 2 weeks prior to scheduled surgery. Regorafenib can be resumed after surgery when the wound is considered to be adequately healed. Discontinue regorafenib in patients with wound dehiscence.

Embryo-Fetal Toxicity

Regorafenib was both embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose. Malformations affected the skeletal, cardiovascular and genitourinary systems.

Fetal harm may result if regorafenib is taken by a pregnant woman. If a patient becomes pregnant while taking regorafenib, they should be made aware of the potential dangers to the fetus.

Special Populations

Pregnancy

Pregnancy Category D. Regorafenib can cause fetal harm when administered to a pregnant woman. In the rat and animal model, regorafenib was both embryolethal and teratogenic at doses lower than human exposures at the recommended dose. An increased incidence of cardiovascular, genitourinary and skeletal malformations was noted. If a patient becomes pregnant while taking regorafenib, they should be made aware of the potential dangers to the fetus.

Nursing mothers

It is not known if regorafenib or its metabolites are excreted in human milk, but this is the case in rats. Due to the potential for serious adverse events in nursing infants, the decision to stop nursing or stop regorafenib should be made, taking into account the importance of the drug to the mother.

Geriatric use

The regorafenib clinical trials (n = 632) included 37% of patients aged 65 and over and 8% of patients aged 75 and over. No differences in safety or efficacy were observed between these and younger patients.

Hepatic impairment

When regorafenib was administered to patients with hepatocellular carcinoma and either mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, there were no clinically important differences noted in the mean exposure of regorafenib or its active metabolites when compared to patients with normal hepatic function. Regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and is not recommended for use in this population.

No dosage adjustment is recommended for patients with mild to moderate hepatic impairment. Closely monitor these patients for adverse reactions.

Renal impairment

When regorafenib was administered to patients with mild renal impairment (defined as CrCl 60-89 ml/min/1.73 m^2), no clinically significant differences in the mean exposure of regorafenib or its metabolites were noted, compared to patients with normal renal function. There is limited data on patients with moderate renal impairment (CrCl 30-59 ml/min/1.73 m^2) and no data on those with severe renal impairment or end-stage renal disease.

No dosage adjustment is recommended for patients with mild renal impairment.

Male & Female Reproductive Potential

Use of effective contraception is recommended during treatment and for up to 2 months after therapy completion.

Although there is no data on the effect of regorafenib on human fertility, animal studies demonstrate that it can impair male and female fertility.

Postmarketing Safety Experience (Optional)

None to report.

Sentinel Events

Serious adverse events that occurred in the regorafenib-treated arm of the CORRECT trial included pneumonia (n=2), gastrointestinal bleeding (n=2), intestinal obstruction (n=1), pulmonary hemorrhage (n=1), seizure (n=1) and sudden death (n=1).

Grade 5 adverse events were noted in 5% (n = 7) regorafenib-treated patients and 5% (n = 3) in the placebo group. In three patients, the events were deemed to be drug-related. Two patients

receiving regorafenib developed cardiac arrest and hepatic failure, while one patient receiving placebo developed fatigue.

Serious adverse events that occurred in the regorafenib-treated arm of the GRID trial included abdominal pain (n=5), fever (n=3) and dehydration (n=3).

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name regorafenib: sorafenib, sunitinib, rituximab, axitinib, crizotinib, dasatinib, imatinib, nilotinib, ruxolitinib, vemurafenib, ranibizumab

LA/SA for trade name Stivarga: Sustiva, Stelara

Drug Interactions

Drug-Drug Interactions

Effect of Strong CYP3A4 Inducers on Regorafenib

Administration of a strong CYP3A4 inducer (rifampin) with a 160 mg dose of regorafenib reduced the mean exposure of regorafenib, increased the mean exposure of the active metabolite M-5 and resulted in no change in the mean exposure of the active metabolite M-2.

Avoid concomitant use of strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital and St. John's Wort).

Effect of Strong CYP3A4 Inhibitors on Regorafenib

Administration of a strong CYP3A4 inhibitor (ketoconazole) with a 160 mg dose of regorafenib increased the mean exposure of regorafenib, decreased the mean exposure of the active metabolites, M-2 and M-5.

Avoid concomitant use of strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole).

Drug-Lab Interactions

None known.

Drug-Food Interactions

A food-effect study was conducted in healthy men who received a single dose of regorafenib under three separate conditions: fasted state, high-fat meal, low-fat meal. A high-fat meal, consisting of 945 calories and 54.6 g fat, increased the mean AUC by 48% and decreased the mean AUC of the active metabolites (M-2 and M-5) by 20 and 51% as compared to the fasted state. Given with a low-fat meal, consisting of 319 calories and 8.2 g fat, increased the mean AUC of regorafenib, M-2 and M-5 by 36, 40 and 23% as compared to fasted conditions.

Acquisition Costs

Please refer to the last page for VA drug acquisition costs. Prices shown in this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

Pharmacoeconomic Analysis

None published.

Conclusions

Regorafenib received FDA approval for heavily pretreated patients with metastatic colorectal cancer who have exhausted all prior treatment options. Patients treated with regorafenib had extended their overall survival rate by 1.4 months, a difference that is statistically significant, yet modest in effect. The clinical benefit of regorafenib was accompanied with toxicity as evidenced by the higher rates of treatment-related adverse events, dose-modifications and drug discontinuations due to adverse events. Although HR-QOL was evaluated as a tertiary endpoint, consideration should be given to the similar deterioration in QOL noted between the regorafenib and placebo arms.

Table 1. Determining Clinical Benefit in mCRC

Outcome in clinically significant area: mCRC	mCRC: Median OS 6.4 vs. 5 months mCRC: Median PFS 1.9 vs. 1.7 months
Effect Size	HR 0.77; 95% CI 0.64-0.94; p=0.0052 for OS HR 0.49; 95% CI 0.42-0.58; p<0.0001 for PFS
Potential Harms	Grade 3-4 toxicity includes asthenia/fatigue (15 vs. 9%); HFSR/PPE (17 vs. 0%); Diarrhea (8 vs. 2%); HTN (8 vs. <1%); Rash (6 vs. <1%)
Net Clinical Benefit	Minimal (modest benefit; high toxicity)

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Regorafenib received FDA-approval for the treatment of locally advanced, unresectable or metastatic GIST in patients who have received prior treatment with imatinib mesylate and sunitinib malate. Prior to this, there had been no other FDA-approved therapy for this indication. Results from the GRID trial indicate that there was no benefit in overall survival, likely affected by crossover of 85% of patients in the placebo arm, but a benefit in PFS that was statistically

significant. This potential benefit should be considered along with the rates of grade 3 and 4 toxicity. As noted by the secondary endpoints of ORR and DCR, regorafenib may have a disease-stabilizing effect. Quality of life data on this study population would be helpful to determine if the improvement in PFS was accompanied with an improvement in patient-reported outcomes. At the present time, this information is not known.

Table 2. Determining Clinical Benefit in GIST

Outcome in clinically significant area: GIST	GIST: Median PFS 4.8 vs. 0.9 months 85% crossed over to Regorafenib arm; The median PFS for those crossover patients was ~ 5 months. No difference in OS: 22 vs. 26 events
Effect Size	HR 0.27; 95% CI 0.19-0.39; p<0.0001 for PFS HR 0.77; 95% CI 0.42-1.41; p=0.199 for OS
Potential Harms	Grade 3-4 toxicity includes HFSR (20 vs. 0%); HTN (23 vs. 3%), Diarrhea (5 vs. 3%)
Net Clinical Benefit	Minimal (modest benefit; high toxicity)

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

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Appendix 1: Approval Endpoints

Table 1 . A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.

Appendix 2: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to present) using the search terms <regorafenib > and <Stivarga >. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Table 1. Regorafenib Clinical Trials in Metastatic Colorectal Cancer (mCRC) & Gastrointestinal Stromal Tumor (GIST)

Citation Design Analysis type N Setting Funding source	Eligibility Criteria	Interventions/Endpoints	Patient Population Profile	Efficacy Results	Safety
Regorafenib in mCRC					
Grothey (2012)[2] CORRECT study R, PC, phase 3 114 centers in 16 countries North America, Europe, Asia, Australia N = 760 patients Regorafenib 500 Placebo 253	**Inclusion criteria** • Aged ≥ 18 yrs • Adenocarcinoma of colon or rectum • Received standard therapies that included fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab; cetuximab or panitumumab if KRAS-WT tumors • ECOG PS 0,1 • Life expectancy ≥ 3 months • Adequate bone marrow, liver and renal function **Exclusion criteria** • CHF NYHA ≥ class 2 • Unstable angina • New-onset angina • MI < 6 months prior to study start • Cardiac arrhythmia requiring anti-arrhythmic therapy (beta blockers, digoxin permitted) • Uncontrolled HTN • Pheochromocytoma • TEE within 6 months • HIV • Chronic hep B or C • Seizure disorder • Symptomatic brain met or meningeal tumors unless > 6 months from definitive therapy • Hx of organ allograft • Hx of bleeding diathesis • Non-healing wound • Dehydration ≥ grade 1 • Interstitial lung	Rand 2:1 Arms: Regorafenib (R) 160 mg PO daily x 3 weeks; Repeat every 4 weeks vs. Placebo Treatment until PD; No crossover allowed Follow-up every 2 wks; tumor response assessed every 8 weeks with RECIST Primary endpoint: OS Secondary: PFS, ORR, DCR, safety Tertiary: DOR, SD, HRQOL	Regorafenib vs. P Median age 61 yrs (54-68 yrs) Sex: male 62 vs. 60% Race: white 79%; Asian 14% ECOG PS 0: 55% ECOG PS 1: 45% KRAS pos: 54 vs. 62% BRAF neg: 96 vs. 98% #prior tx for mCRC: 1-2: 27 vs. 25% 3: 25 vs. 28% ≥ 4: 49 vs. 47% Median time from dx: 31 vs. 30 months (range, 20-46)	Regorafenib vs. Placebo Median OS: 6.4 vs. 5 months (HR 0.77; 95% CI 0.64-0.94; p=0.0052) Greater effect on colon (HR 0.70; 95% CI 0.56-0.89) vs. rectal cancer (HR 0.95; 95% CI 0.63-1.43) Median PFS: 1.9 vs. 1.7 months (HR 0.49; 95% CI 0.42-0.58; p< 0.0001) ORR: 1.0 vs. 0.4%; p=0.19 No CR DCR: 41 vs. 15%; p<0.001 Median duration SD: 2 vs. 1.7 months Median duration of treatment: 1.7 vs. 1.8 months Planned dose received: 79 vs. 90% Dose-modifications: 76 vs. 38%	Regorafenib vs. Placebo Treatment-related AE: 93 vs. 61% **Most Common** R: fatigue, HFSR P: fatigue, anorexia **Serious** (gr 3, 4) Grade 3: 51 vs. 12% Grade 4: 3 vs. 2% R: HFSR, fatigue, diarrhea, HTN, rash P: fatigue **Deaths** Tx-related deaths: 2 vs. 1% R: pna, GI bleed, GI obstruction, pulm hemorrhage, seizure, sudden death P: pna, sudden death Thromboembolism: 2 vs. 2% AE → dose modification: 67 vs. 23% **HRQOL via EORTC QLQ-C30:** R: 62.6 (SD 21.7) baseline to 48.9 (21.6) P: 64.7 (SD 22.4) baseline to 51.9 (23.9) Deterioration in QOL was similar in both groups. **EQ-5D health utility vis VAS:** R: 65.4 (19.6) baseline to 55.5 (20.4) P: 65.8 (20.5) baseline to 57.3 (21.6) No clinically meaningful difference

Citation Design Analysis type N Setting Funding source	Eligibility Criteria	Interventions/Endpoints	Patient Population Profile	Efficacy Results	Safety
	disease • Persistent proteinuria ≥ grade 3 • Malabsorption				between start to end of treatment in either group.
Regorafenib in GIST Clinical Trials					
Demetri (2012)[3] GRID study R, PC, MC, phase 3 57 centers in 17 countries (Austria, Belgium, Canada, China, Finland, France, Germany, Israel, Italy, Japan, Netherlands, Poland, Singapore, South Korea, Spain, UK, USA) N = 199 patients Regorafenib 133 Placebo 66	**Inclusion criteria** • Aged ≥ 18 yrs • Metastatic and/or unresectable GIST • Prior imatinib and sunitinib • At least 1 measurable lesion • ECOG PS 0,1 • Adequate bone marrow, liver and renal function **Exclusion criteria** • Prior tx w/VEGFR inhibitor other than sunitinib • Major surgery w/in 28 days of start • Pregnancy/breast-feeding • CHF NYHA ≥ class 2 • Unstable angina • New-onset angina • MI < 6 months prior to study start • Cardiac arrhythmia requiring anti-arrhythmic therapy (beta blockers, digoxin permitted) • Uncontrolled HTN • Pheochromocytoma • Arterial TE w/in 6 months • VTE w/in 3 months • LVEF < 50% • HIV • Chronic hep B or C • Seizure disorder • Symptomatic brain met or meningeal tumors unless > 6 months from definitive therapy • Hx of organ allograft • Hx of bleeding	Rand 2:1 Arms: Regorafenib (R) 160 mg PO daily x 3 weeks; Repeat every 4 weeks vs. Placebo Treatment until PD or unacceptable toxicity; At PD, crossover to R was permitted Tumor assessments at baseline, then every 4 wks x 3 months, every 6 wks x 3 months, then every 8 wks Primary endpoint: PFS Per RECIST assessed by blinded central radiology reviewers Secondary: OS, TTP, ORR, DCR Exploratory: HRQOL, PK, secondary PFS during open-label treatment, biomarker assessment	Regorafenib vs. P Median age 60 (51-67) vs. 61 yrs (48-66 yrs) Sex: male 64% Race: white 68%; Asian 25% ECOG PS 0: 55 vs. 56% ECOG PS 1: 45 vs. 44% #prior tx for GIST: 2: 56 vs. 59% > 2: 44 vs. 41% Duration imatinib tx: ≤ 6 mos: 14 vs. 6% 6-18 mos: 20 vs. 11% > 18 mos: 67 vs. 83%	Regorafenib vs. Placebo 56 (85%) of placebo patients crossed over to R Mean treatment duration: 20.2 vs. 9.1 wks Mean daily dose: 146.8 vs. 160 mg Planned dose received: 78 vs. 84% Median PFS: 4.8 vs. 0.9 months (HR 0.27; 95% CI 0.19-0.39; p<0.0001) Median PFS in crossover pts: 5.0 months No difference in OS: 22 vs. 26 events (HR 0.77; 95% CU 0.42-1.41; p=0.199) All subgroups showed benefit from R, except for the subset of pts with imatinib duration < 6 months ORR: 4.5 vs. 1.5% No complete responses were noted; SD: 71.4 vs. 33.3% DCR: 52.6 vs. 9.1% Exploratory analyses were not reported.	Regorafenib vs. Placebo Drug-related AEs: 98 vs. 69% Most common AE (any grade): HFSR: 56 vs. 14% AE (grade 3-5): 61 vs. 14% R: HTN (23%), HFSR (20%), diarrhea (5%) Drug-related grade 5 events: 2 vs. 2% R: cardiac arrest, hepatic failure P: fatigue Serious AE: 29 vs. 21% R: abdominal pain, fever, dehydration P: fatigue, pain Dose-modifications: 72 vs. 26% DC due to AE: 6 vs. 8%

Citation Design Analysis type N Setting Funding source	Eligibility Criteria	Interventions/Endpoints	Patient Population Profile	Efficacy Results	Safety
	diathesis • Non-healing wound • Dehydration ≥ grade 1 • Interstitial lung disease • Persistent proteinuria ≥ grade 3 • Malabsorption • Pleural effusion/ ascites w/resp compromise				

R, randomized; PC, placebo-controlled; R, regorafenib; P, placebo; KRAS-WT; KRAS wild-type; ECOG, Eastern Cooperative Oncology Group; CHF, congestive heart failure; NYHA, New York Heart Association; MI, myocardial infarction; TEE, thromboembolic event; LVEF, left ventricular ejection fraction; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; PD, progressive disease; DCR, disease control rate; DOR, duration of response; SD, stable disease; HRQOL, health-related quality of life; HRSR, hand-foot skin reaction; TTP, time to progression; PK, pharmacokinetic